# Undisclosed NIH funding for patents on eteplirsen (brand name: Exondys 51)

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## Introduction

Knowledge Ecology International (KEI) has discovered what appears to be a failure to disclose National Institutes of Health (NIH) research funding on four patents granted to Stephen Wilton, Sue Fletcher and Graham McClorey, assigned to the University of Western Australia. The four patents have the same inventors, the same title and the same priority date (June 28, 2004). Two of the four Wilton *et al.* patents are listed in the FDA Orange Book for the drug marketed by Sarepta Therapeutics as Exondys 51 (INN eteplirsen), a treatment for Duchenne Muscular Dystrophy (DMD).

From 2004 to 2012, Stephen Wilton was the principal investigator for eight projects awarded $1,508,360 in total funding by the U.S. NIH, National Institute of Neurological Disorders and Stroke (NINDS) for research on antisense oligonucleotides and Duchenne muscular dystrophy (DMD). The grants were directly related to the four Wilton *et al.* patents.

KEI has also determined there was a failure to disclose federal research funding for patent 9,416,361, which lists Patrick Iversen and Robert Hudziak as inventors, and is assigned to Sarepta Therapeutics. This patent is also listed in the FDA Orange Book for Exondys 51.

The Sarepta price for Exondys 51 is excessive, and the high cost has created significant access barriers and hardships for patients. According to one analyst who reviewed insurance claims, the annual cost of the treatment for some patients will be in the range of $750,000 to $1.5 million, which does not include other drugs that may be required for treatment.[1]

[1] Katie Thomas, Insurers Battle Families Over Costly Drug for Fatal Disease, *New York Times*. June 22, 2017.

Not all of the patents listed in the FDA Orange Book have identified U.S. government funding, and the drug is protected by the U.S. orphan drug exclusivity through September 19, 2023. However, the failure by inventors to disclose NIH funding provides the United States government with an opportunity to take title to at least five relevant Exondys 51 patents, and to use the ownership of the patents as leverage to lower the price.

KEI also suggests that the NIH and the U.S. Department of Defense review 91 other patents assigned to Sarepta which do not disclose federal research funding.

Finally, this case illustrates an area for potential future cooperation between the United States and other governments, as regards government rights in patents. One patent in the Orange Book for Exondys 51 is assigned to the Academisch Ziekenhuis Leiden in the Netherlands, an institution that receives research funding from the Dutch government and the European Union. The University of Western Australia also claimed DMD-related funding from the Western Australia Medical and Health Research Infrastructure Fund (MHRIF). An agreement among governments on the financing of biomedical R&D (as has been proposed for the World Health Organization), could include provisions for cross-licensing government rights in patents.

## Sarepta Therapeutics

Sarepta Therapeutics is the current name of the firm first known as AntiVirals, Inc. and later as Avi BioPharma.

AntiVirals, Inc. was incorporated in the state of Oregon on July 22, 1980 to develop and commercialize therapeutic products based upon antisense and cancer immunotherapy technology. In 2002, the company was renamed Avi BioPharma. In July 2009, the company moved its headquarters from Portland, Oregon to Bothell, Washington.[2]

In 2012, the company changed its name to Sarepta Therapeutics and moved to Cambridge, Massachusetts, motivated by the need to recruit expertise in rare diseases.[3]

Over time, the company expanded its focus and explored other areas of research, funded through a variety of sources including stock sales, collaborations and government grants and contracts.

[2] Luke Timmerman, AVI Biopharma Bolts from Portland to Seattle to Tap Biotech Talent, *Xconomy*. July 30, 2009.
[3] Luke Timmerman, Sarepta Moves From Seattle to Boston for the Talent, *Xconomy*. September 7, 2012; Don Seiffer, Here's why Sarepta Therapeutics is consolidating in Massachusetts, *Boston Business Journal.* March 9, 2016.

At one point nearly all of the firm's revenue was based upon government contracts and grants, primarily from Department of Defense and the NIH, relating to research on a variety of infectious diseases and on Duchenne muscular dystrophy (DMD).

In 2011, several large research contracts from the Department of Defense began to wind down.

## What does eteplirsen do?

Eteplirsen, once named AVI-4658, is a drug sold by Sarepta Therapeutics under the trade name Exondys 51 for the treatment of Duchenne muscular dystrophy (DMD).

The FDA approved the sale of of Exondys 51 on September 19, 2016. The FDA press release about the approval offered this description:[4]

> The U.S. Food and Drug Administration today approved Exondys 51 (eteplirsen) injection, the first drug approved to treat patients with Duchenne muscular dystrophy (DMD). Exondys 51 is specifically indicated for patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, which affects about 13 percent of the population with DMD. . .
>
> DMD is a rare genetic disorder characterized by progressive muscle deterioration and weakness. It is the most common type of muscular dystrophy. DMD is caused by an absence of dystrophin, a protein that helps keep muscle cells intact. The first symptoms are usually seen between three and five years of age, and worsen over time. The disease often occurs in people without a known family history of the condition and primarily affects boys, but in rare cases it can affect girls. DMD occurs in about one out of every 3,600 male infants worldwide.
>
> People with DMD progressively lose the ability to perform activities independently and often require use of a wheelchair by their early teens. As the disease progresses, life-threatening heart and respiratory conditions can occur. Patients typically succumb to the disease in their 20s or 30s; however, disease severity and life expectancy vary.

Katie Thomas, writing for the New York Times, said:[5]

> "Exondys 51 may be helping protect muscle cells from deterioration by producing a form of dystrophin, a protein largely lacking in those with the genetic mutation. The

[4] FDA Press Release, FDA grants accelerated approval to first drug for Duchenne muscular dystrophy, September 19, 2016.
[5] Katie Thomas, Insurers Battle Families Over Costly Drug for Fatal Disease, *New York Times*. June 22, 2017.

> boys typically need wheelchairs by their teenage years, and their hearts and lungs eventually give out. Between 9,000 and 12,000 people are estimated to be living with Duchenne in the United States; about 13 percent have the genetic mutation receptive to the new drug."

## Controversy over the FDA approval of Exondys 51

The approval of Exondys 51 was controversial because of the small number of the patients in the clinical trials, and because a review panel had narrowly recommended against the approval before being overruled by FDA Commissioner Dr. Janet Woodcock.

Below are some of the commentary regarding the approval of Exondys 51.

Editorial, "Railroading at the FDA," *Nature Medicine*. Vol. 22, Num. 1193 (2016). doi:10.1038/nm.4234

> "In the words of one FDA committee member, Exondys lowers the agency's evidentiary standard for drug effectiveness 'to an unprecedented nadir.'"

Sy Mukherjee, "The FDA Just Made Its Most Controversial Drug Approval of the Year," *Fortune*. September 19, 2016.

> "What's striking about the FDA approval is that it overrules its own scientific advisers. An independent advisory panel voted against recommending approval in a highly polarized 7-6 vote in April, adding that the company's clinical trials for the treatment were poorly designed. But Sarepta had two key allies on its side that buttressed the biotech's chances and led to Monday's reversal: the DMD patient community, which flooded the ill-fated April FDA panel meeting on the therapy with highly personal, heart-wrenching testimony, and Dr. Janet Woodcock, the director of the FDA's Center for Drug Evaluation and Research (CDER)."

John Carroll, "FDA officials: There was "no scientific basis" for Duchenne drug OK as Sarepta complained of "dire financial" condition," *Endpoints News.* November 4, 2016.

> "Two senior FDA officials mounted a vehement assault on Janet Woodcock's decision to push through an approval of Sarepta's Duchenne muscular dystrophy drug Exondys 51. New documents posted by the FDA, including a round of memos on the issue in September, warned FDA Commissioner Robert Califf that he was allowing an approval even though Woodcock had not considered all the analysis they had done to underscore the company's weak case, adding that there was no scientific basis to conclude that the drug was reasonably likely to benefit patients."

## The high price of Exondys 51 is a barrier to access

After the approval of Exondys 51, the editors of *BIOCentury* defended the accelerated approval but expressed concern over the price:[6]

> "We still believe accelerated approval was the right decision. Unfortunately, judging by the $300,000 annual net cost for a drug that at this point is only "reasonably likely" to produce a clinical benefit, it looks like Sarepta is continuing to get it wrong. Unless the company engages in risk-sharing or pay-for-performance deals with payers, the high price will prevent broad access to the drug -- and giving patients broad access was the best reason to grant this drug accelerated approval."

It appears, however, that the costs are far higher than $300,000 per year.

This drug, administered once weekly, is available either in a 2 ml or 10 ml vial depending on the weight of the patient. The 2 ml vial costs $1,600 whilst the 10 ml vial costs $8,000.

The 2017 article by Katie Thomas in the New York Times reported that an analysis by Prime Therapeutics estimated the average cost of the drug, at its list price, for the twelve patients in the main clinical trial cited by the FDA when the drug was approved, at $750,000 each, more than double the $300,000 per child figure announced by the manufacturer.[7]

> "I'm reading a lot of denial letters," said Christine McSherry, who until recently served as executive director of the Jett Foundation, an advocacy group that guides families through the insurance appeal process. Her insurer, Blue Cross Blue Shield of Massachusetts, is covering the drug for her son, Jett, through next April. "It's very disheartening to have worked that hard, and to have sacrificed that much, and to now have to battle the insurance companies."
>
> The drug's high cost is driving the resistance. While the drug manufacturer, Sarepta, has said Exondys 51 costs about $300,000 a year per child, the price, based on a child's weight, can be much higher. For the dozen boys in the main clinical trial, the average list price would be more than double Sarepta's quote — $750,000 each, according to an analysis by the drug benefit firm Prime Therapeutics.

[6] Susan Schaeffer (Editor, BioCentury), Erin Mccallister (Senior Editor), And Steve Usdin (Washington Editor), Wrong Again: Why Sarepta's $300k Price For Dmd Drug Invalidates Reasons For Accelerated Approval, *BioCentury*. September 26, 2016.
[7] Katie Thomas, Insurers Battle Families Over Costly Drug for Fatal Disease, *New York Times*. June 22, 2017.

Thomas reported that for some patients, the cost is as high as $1.5 million per year, or more than $4,000 per day, and that patients are concerned that the treatment will also require the use of other expensive drugs.[8]

> Sarepta's executives have claimed in statements that the average price for Exondys 51 is $300,000 per patient per year.
>
> "That's not accurate," said David Lassen, the chief clinical officer at Prime Therapeutics, which manages the drug plans for more than 20 million Americans. "Based on just the few claims that we've evaluated, we think that's low." He cited a range from $750,000 to $1.5 million a year, far greater than breakthrough drugs like, for instance, cystic fibrosis treatments sold by Vertex that cost more than $250,000 a year.
>
> Sarepta contends that the $300,000 estimate is a net price, accounting for discounts to insurers and the fact that not everyone will follow the weekly regimen. It also includes the assumption that younger boys who weigh less will begin taking the drug. "What we have seen is that for some of the older, sicker boys who have been using it, the price is more," said Dr. Ed Kaye, the chief executive of Sarepta.
>
> Many Duchenne parents worry that insurers will balk if other costly drugs are approved to complement the treatment from Exondys 51. Already, they are reeling from the decision by PTC Therapeutics to price a once-cheap steroid, deflazacort, at about $35,000 per year. Many families had been importing it for about $1,600 a year.

## Exondys 51 sales

Exondys 51 was approved for sale on September 19, 2016. Net sales from product sales are as follows:

**Table 1: Exondys 51 sales**

| Period | Sales |
|---|---|
| 2016 | $ 5,421 |
| | |
| 2017:Q1 | $16,340 |
| 2017:Q2 | $35,011 |
| 2017:Q3 | $45,954 |
| 2017:Q4 | $57,277 |

[8] *Ibid.*

## The FDA Orange Book patents on Exondys 51

On March 14, 2018, there were five patents listed in the Orange Book for Exondys 51. Two were assigned to the University of Western Australia, two were assigned to Sarepta Therapeutics in Cambridge, Massachusetts, and one jointly to an academic institution and a biomedical company both in Leiden, Netherlands.

**Table 2: FDA Orange Book patents on Exondys 51**

| Patent Number | File date | Grant date | Priority Date | Expiration | Inventors | Assignee |
|---|---|---|---|---|---|---|
| 8486907 | Oct 11 2011 | Jul 16 2013 | Jun 28, 2004 [AU] | Jun 28 2025 | Wilton; Stephen Donald (Applecross, AU), Fletcher; Sue (Bayswater, AU), McClorey; Graham (Bayswater, AU) | The University of Western Australia |
| 9018368 | Jun 26 2014 | Apr 28 2015 | Jun 28, 2004 [AU] | Jun 28 2025 | Wilton; Stephen Donald (Applecross, AU), Fletcher; Sue (Bayswater, AU), McClorey; Graham (Bayswater, AU) | The University of Western Australia |
| 9243245 | Apr 26 2010 | Jan 26 2016 | Oct 26, 2007 [EP] | Oc 27, 2028 | De Kimpe; Josephus Johannes (Utrecht, NL), Platenburg; Gerard Johannes (Voorschoten, NL), Van Deutekom; Judith Christina Theodora (Dordrecht, NL), Aartsma-Rus; Annemieke (Hoofddorp, NL), Van Ommen; Garrit-Jan Boudewijn (Amsterdam, NL) | Academisch Ziekenhuis Leiden (Leiden, NL), BioMarin Technologies B.V. (Leiden, NL) |
| 9416361 | Nov 6 2014 | Aug 16 2016 | May 4 2000 | May 4, 2021 | Iversen; Patrick L. (Corvallis, OR), Hudziak; Robert (Blodgett, OR) | Sarepta Therapeutics, Inc. |
| 9506058 | Mar 14 2014 | 11/29/ 2016 | Mar 15 2013 | Mar 14, 2034 | Kaye; Edward M. (Cambridge, MA) | Sarepta Therapeutics, Inc. |

The 2017 Sarepta Therapeutics Securities and Exchange Commission (SEC) 10-K annual report lists seven patents for eteplirsen (Exondys 51), including two earlier patents (7,807,816 and 7,960,541) assigned to the University of Western Australia that are currently not listed in the FDA Orange Book. The two earlier UWA patents have the same inventors, title and priority date as the two newer UWA ones.

**Table 3: Patents for *eteplirsen* listed in the Sarepta Therapeutics 10-K**

| Patent | Type | Expiration | Owner |
|---|---|---|---|
| 7,807,816 | Composition of Matter | February 23, 2026 | UWA |
| 7,960,541 | Composition of Matter | June 28, 2025 | UWA |
| 8,486,907 | Methods of Use | June 28, 2025 | UWA |
| 9,018,368 | Composition of Matter | June 28, 2025 | UWA |
| 9,243,245 | Methods of Use | October 27, 2028 | BioMarin/AZL |
| 9,416,361 | Composition of Matter | May 4, 2021 | Sarepta |
| 9,506,058 | Methods of Use | March 14, 2034 | Sarepta |

## Wilton, Fletcher and McClorey patents that failed to disclose federal funding

The four patents assigned to the University of Western Australia for antisense oligonucleotides for inducing exon skipping are listed in Table 4.

### Table 4: Four Wilton *et al*. patents for antisense oligonucleotides for inducing exon skipping that failed to disclose NIH grants

| Patent number | Date filed | Date granted | Priority date | Title |
|---|---|---|---|---|
| 7,807,816 | 01/05/2006 | 10/05/2010 | 6/28/2004 | Antisense oligonucleotides for inducing exon skipping and methods of use thereof |
| 7,960,541 | 8/20/2010 | 6/14/2011 | 6/28/2004 | Antisense oligonucleotides for inducing exon skipping and methods of use thereof |
| 8,486,907 | 10/11/2011 | 7/16/2013 | 6/28/2004 | Antisense oligonucleotides for inducing exon skipping and methods of use thereof |
| 9,018,368 | 6/26/2014 | 4/28/2015 | 6/28/2004 | Antisense oligonucleotides for inducing exon skipping and methods of use thereof |

The patents in Table 4 have different filing and grant dates, but the exact same title and the same priority date of June 28, 2004.

## The related and undisclosed research grants from National Institute of Health

According to the National Institutes of Health RePORTER database, Stephen Wilton was the principal investigator for eight NIH funded projects awarded to the University of Western Australia, involving $1,508,360. The projects were from the National Institute of Neurological Disorders and Stroke (NINDS), for fiscal years 2004 to 2012.

### Table 5: The NIH grants for antisense oligonucleotides

| Grant number | Title | PI | Budget Start Date | Budget End Date | Agency |
|---|---|---|---|---|---|
| 5 R01 NS044146 01A2 | ANTISENSE OLIGONUCLEOTIDE SUPPRESSION OF DMD | WILTON, STEPHEN D | 1/1/04 | 12/1/04 | NINDS |
| 5 R01 NS044146 02 | ANTISENSE OLIGONUCLEOTIDE SUPPRESSION OF DMD | WILTON, STEPHEN D | 1/1/05 | 12/31/05 | NINDS |
| 5 R01 NS044146 03 | ANTISENSE OLIGONUCLEOTIDE SUPPRESSION OF DMD | WILTON, STEPHEN D | 1/1/06 | 12/31/06 | NINDS |

| | | | | | |
|---|---|---|---|---|---|
| 5 R01 NS044146 04 | ANTISENSE OLIGONUCLEOTIDE SUPPRESSION OF DUCHENNE MUSCULAR DYSTROPHY | WILTON, STEPHEN D | 1/1/07 | 12/31/07 | NINDS |
| 5 R01 NS044146 05A1 | ANTISENSE OLIGONUCLEOTIDE SUPPRESSION OF NON-DELETION DMD CAUSING MUTATIONS | WILTON, STEPHEN D | 4/15/09 | 3/31/10 | NINDS |
| 5 R01 NS044146 06 | ANTISENSE OLIGONUCLEOTIDE SUPPRESSION OF NON-DELETION DMD CAUSING MUTATIONS | WILTON, STEPHEN D | 4/1/10 | 3/31/11 | NINDS |
| 5 R01 NS044146 07 | ANTISENSE OLIGONUCLEOTIDE SUPPRESSION OF NON-DELETION DMD CAUSING MUTATIONS | WILTON, STEPHEN D | 1-Apr-2011 | 3/31/12 | NINDS |
| 5 R01 NS044146 08 | ANTISENSE OLIGONUCLEOTIDE SUPPRESSION OF NON-DELETION DMD CAUSING MUTATIONS | WILTON, STEPHEN D | 4/1/12 | 3/31/13 | NINDS |

The titles of all eight projects mention antisense oligonucleotides, a form of technology whereby a sequence complementary to a specific mRNA is used to inhibit expression and prevent the transfer of genetic information from DNA to protein, for the treatment of Duchenne Muscular Dystrophy (DMD).

The abstracts given for the grants are as follows:

### The abstracts for the antisense oligonucleotide grants

**5 R01 NS044146 01A2, 5 R01 NS044146 02, 5 R01 NS044146 03 and 5 R01 NS044146 04**

DESCRIPTION (provided by applicant): The ultimate goal of this project is to develop an antisense oligonucleotide (AO) therapy for Duchenne muscular dystrophy (DMD). Antisense oligonucleotides (AOs) can be used to reduce the severity of DMD by removing specific exons during pre-mRNA splicing, to either by-pass nonsense mutations or restore the reading frame around dystrophin genomic deletions. As a result of the treatment, dystrophin expression would be restored in dystrophic tissue and DMD patients would theoretically manifest only the milder phenotype of Becker Muscular Dystrophy (BMD). This project will explore the design and delivery of AOs to minimize the consequences of disease-causing dystrophin gene mutations. (1) Animal models of muscular dystrophy will be used to develop treatment regimens and assess therapeutic benefits in vivo. (2) AOs will be designed to target the most amenable splicing motifs at relevant exons in the human dystrophin gene transcript and will be evaluated in cultured human muscle cells. Although this approach cannot permanently correct the primary genetic lesion, we propose that repeated administration, preferably through systemic delivery, should be feasible. AO chemistries or modifications to increase stability and/or uptake, optimized for in vivo induction of exon skipping, will be developed and evaluated. Only periodic administration of AOs should be required to maintain therapeutic levels of induced dystrophin in dystrophic muscle. DMD is a serious disorder for which there is no effective treatment. AOs will not cure this devastating condition, however, AO-based splicing intervention has the potential to reduce the severity of DMD so that treated boys should be able to produce some functional dystrophin. This would be expected to moderate the severity of DMD and improve the quality of life for patients and their families.

**5 R01 NS044146 05A1, 5 R01 NS044146 06, 5 R01 NS044146 07 and 5 R01 NS044146 08**

DESCRIPTION (provided by applicant): Duchenne muscular dystrophy (DMD) is a fatal X-linked muscle-wasting disorder caused by protein truncating mutations in the dystrophin gene. Antisense oligomer induced removal of an exon carrying a nonsense mutation, or exons flanking frame-shifting deletions, the most common type of DMD mutation, has been shown to generate an in-frame message and an internally deleted, but functional protein. Becker muscular dystrophy (BMD) is an allelic disorder typically caused by in-frame deletions of one or more exons, most commonly in the first two thirds of the gene. The severity of BMD varies from borderline DMD to asymptomatic, and the dystrophin genes in mildly affected BMD patients provide an indication of functional exon combinations. At least one third of DMD cases result from duplications, micro-insertions/deletions and single base changes that alter splice site recognition or cause premature termination of translation. This project will address the design and application of antisense oligomers for induced exon skipping, for those DMD cases caused by non-deletion mutations. Patient cell lines will be transfected with test compounds and exon skipping assessed. Exon skipping strategies will be modified to maximize induced dystrophin quality and quantity, as permitted by the context of each particular dystrophin gene lesion. The specific aims are to: 7 Optimise antisense oligomers to remove exons carrying sequence variations (disease-causing or neutral polymorphims) that would otherwise compromise exon skipping. 7 Develop exon skipping strategies appropriate to DMD cases caused by pseudo-exon incorporation or duplications of one or more exons. 7 Develop transient animal models to identify functionally significant dystrophin domains, according to exon boundaries, to facilitate design of optimal exon skipping strategies. PUBLIC HEALTH RELEVANCE: Duchenne muscular dystrophy is a relentlessly progressive, fatal disease for which there is no effective treatment. Specific exon removal has the potential to greatly reduce the severity of DMD, and restoration of dystrophin expression, even of partial function in a DMD patient is expected to result in a BMD-like phenotype, and reduce morbidity and extend life expectancy. This application seeks to develop personalised exon skipping therapies for the one third of DMD patients who have non-deletion mutations. Exon skipping should be made available to all patients who could benefit, not only those with the more common exon deletion mutations.

All the patents listed above in Table 4 provide several key terms/words that appear to be the subject matter of the grants, including, to mention a few:

- Antisense Oligonucleotide (ABSTRACT)
- **Exon Skipping** (ABSTRACT)
- Dystrophin gene (ABSTRACT)
- Claim 29 - The method of claim 25, wherein the subject is a human and the muscular dystrophy is **Duchenne muscular dystrophy**. (PAGE 138, PATENT 8,486,907 )
- Claim 28 - The method of claim 25, wherein the subject is a human and the muscular dystrophy is **Becker muscular dystrophy**. (PAGE 138, PATENT 8,486,907)
- These **Duchenne muscular dystrophy** gene defects are typically nonsense mutations or genomic rearrangements such as **deletions**, **duplications** or **micro-deletions** or **insertions** that disrupt the reading frame. (PAGE 23, PATENT 8,486,907)
- The acceptor and donor **splice sites** have consensus sequences of about 16 and 8 bases respectively (PAGE 4, PATENT 8,486,907)
- FIG. 2. Diagrammatic representation of the concept of antisense oligonucleotide induced **exon skipping** to by-pass disease-causing mutations (not drawn to scale). The hatched box represents an exon carrying a mutation that prevents the **translation** of the rest of the **mRNA** into a protein. The solid black bar represents an **antisense**

> **oligonucleotide** that prevents inclusion of that **exon** in the mature **mRNA**. (PAGE 5, PATENT 9,018,368)

In 2008, the University of Western Australia licensed its patent rights to Avi BioPharma.

> **University of Western Australia**
> In November 2008, we entered into an exclusive license with the University of Western Australia, or UWA, for certain patents and technical information relating to the use of certain antisense sequences for the treatment of DMD. The license grants us specific rights to the treatment of DMD by inducing the skipping of certain exons defined in the agreement.[9]

## The Iversen patent that did not disclose federal funding

KEI has discovered that the one patent assigned to Sarepta Therapeutics for Exondys 51 also appears to have failed to report federal funding.

**Patent number: 9,416,361**

| | |
|---|---|
| Title: | Splice-region antisense composition and method |
| Inventors: | Iversen; Patrick L. (Corvallis, OR), Hudziak; Robert (Blodgett, OR) |
| Filed: | November 6, 2014 |
| Granted: | August 16, 2016 |
| Priority: | May 4, 2000 |
| Assignee: | Sarepta Therapeutics, Inc. (Cambridge, MA) |

The NIH funded a series of research projects relevant to this invention from June 1997 to March 31, 2001, a period which spans from before to right after the priority date of the invention. The title of each project was, “Gene Expression Modulators To Control Drug Metabolism.” Patrick Iversen was listed as the principal investigator. The first project was a grant to the University of Nebraska Medical Center, and the last three were to Oregon State University.

**Table 6: Four relevant Iversen projects funded by the NIH from 1997 to 2000**

| Fy | Project number | PI | Receipteint | Cost in FY |
|---|---|---|---|---|
| 1997 | 1R01GM054871-01A1 | Iversen, Patrick L. | University Of Nebraska Medical Center | 169,248 |
| 1998 | 7R01GM054871-02 | Iversen, Patrick L. | Oregon State University | $114,280 |

[9] https://www.sec.gov/Archives/edgar/data/873303/000119312511066190/d10k.htm

| | | | | |
|---|---|---|---|---|
| 1999 | 5R01GM054871-03 | Iversen, Patrick L. | Oregon State University | $106,765 |
| 2000 | 5R01GM054871-04 | Iversen, Patrick L. | Oregon State University | $110,076 |

The abstracts were the same for all four projects and were as follows:

> DESCRIPTION (Adapted from Investigator's Abstract): The purpose of this proposal is to exploit the potential for gene-specific activities of synthetic **oligonucleotides** (ODNs) in an animal model involving drug metabolism. The mechanistic actions of nuclease resistant ODNs include sequence-specific interactions with nucleic acids as antigene or antisense molecules or with transcriptional regulatory proteins in a manner that mimics the genomic cis-elements resulting in the modulation of gene expression. The investigators intend to test the hypothesis that optimal **oligonucleotide** structures can be identified that modulate the expression of cytochrome P450 isoforms in vivo. Further, that gene expression modulation will provide insights into the regulation of these genes' expression and their reliance on endogenous substrates and extrahepatic expression. **In vivo** studies are proposed because ODN entry into and distribution within the cell is not equivalent between studies conducted in cultured cells and that observed in intact animals. The specific aims of these studies are to: 1) identify optimal **oligonucleotide** structures for **antisense**, antigene, ribozyme and transcriptional regulation of gene expression in vivo, 2) evaluate the mechanism of action of these modulators of gene expression, 3) identify in **in vivo** modulators a broad spectrum of phase I drug metabolizing enzymes including rat CYP1A1, CYP2B1, CYP2B2, CYP2C11, CYP2E1, **CYP3A2** and CYP4A1 and 4) evaluate these gene expression modulators in context dependent expression created by sex hormones, circadian rhythm, xenobiotic exposure and extrahepatic organs. The advantages of this model system are that 1) constitutive gene expression is monitored in the absence of disease, 2) the in vivo efficacy is confirmed by **in vitro** analysis of enzyme activities and protein levels directly link the target **mRNA** with observed phenotype, 3) toxicity can be evaluated concomitantly with efficacy, 4) the approach is cost effective, 5) this approach avoids discrepancies that are in cell culture and 6) direct comparison of potency, efficacy and toxicity can be made with linear **phosphorothioate** ODNs. Future studies will involve a more detailed investigation of the role of cytochrome P450 expression in the regulation of radical oxygen sensitive genes in vivo.

The descriptions of the invention in the Iversen patent 9,416,361 include several references which are related to the abstract of the grant. For example, from the text of the patent:

- The **antisense** compound is RNase-inactive, and is preferably a **phosphorodiamidate**-linked morpholino **oligonucleotide**.
- A morpholino **antisense oligonucleotide** composition may be administered in any convenient physiologically acceptable vehicle.
- studies were carried out with rat **CYP3A2** pre-**mRNA** targeted **in vivo** (whole animal). Animals were injected i.p. with 100 .mu.g PMO (as shown in FIG. 3, where Y.sub.1 and Z are oxygen and X is N(CH.sub.3).sub.2) in phosphate buffered saline. The diminished rate of microsomal metabolism of erythromycin O-demethylase was monitored to reflect the expected phenotype caused by the **antisense** inhibition.

Iversen is also listed as the PI for eight other NIH-funded projects, including three grants to Avi Biopharma, which received at least ten NIH-funded projects.

## The 2006 Nature paper

In 2005, the three Australian inventors, Iversen, and Hong Moulton (another researcher for Avi BioPharma) co-authored a paper that was published by *Nature* in 2006, with the title, "Antisense oligonucleotide-induced exon skipping restores dystrophin expression in vitro in a canine model of Duchenne muscular dystrophy (DMD)."[10]

The acknowledgements section in the Nature paper states:

> "This work was funded by Parent Project Muscular Dystrophy, USA, National Institute of Health, USA, National Health and Medical Research Council, Australia, Muscular Dystrophy Association, USA and the Medical and Health Research Infrastructure Fund, Western Australia."

## The 2010 QTDP grants

The Avi BioPharma SEC 10-K report for the fiscal year ended December 31, 2010 reported that the company received five grants from the federal government's Qualifying Therapeutic Discovery Project, or QTDP program, "for our DMD program and infectious disease programs" and that the grant for each application was approximately $244,000.[11]

According to the 10-K report, "the QTDP was part of the March 2010 Patient Protection and Affordable Care Act and provides a tax credit or grant equal to 50 percent of eligible costs and expenses for tax years 2009 and 2010."

## Note on extent of disclosures for other patents assigned to Sarepta Therapeutics

We ran two queries of of the US Patent & Trademark Office Patent Full Text and Image Database to determine the number of patents assigned to Sarepta Therapeutics in total, and among those patents, the number that disclosed federal funding of the invention.

The first query was:

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AN/antivirals OR AN/"avi biopharma" OR AN/sarepta
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[10] G McClorey, H M Moulton, P L Iversen, S Fletcher & S D Wilton, Antisense oligonucleotide-induced exon skipping restores dystrophin expression in vitro in a canine model of DMD, Gene Therapy volume 13, pages 1373–1381 (2006); doi:10.1038/sj.gt.3302800

[11] https://www.sec.gov/Archives/edgar/data/873303/000119312511066190/d10k.htm

Which identified 101 granted patents that were assigned to either “Antivirals” (the original name of the company), “Avi BioPharma” (the second name) or “Sarepta” (the current name).

The second query searched within those 101 identified patents for either a declaration of federal funding, or an assignment to the United States government, the Department of Defense, the Department of Health and Human Services, or the U.S. Army.

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(AN/antivirals OR AN/"avi biopharma" OR AN/sarepta) AND
(GOVT/government OR AN/defense OR AN/army OR AN/united OR
AN/health)
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The second query identified ten of the Antivirals/Avi BioPharma/Sarepta patents that matched criteria, including four patents that disclosed grants (two each from HHS and DoD) and six patents with joint assignments to a federal agency, of which three were jointly assigned with HHS and three others with the U.S. Army.

A list of the patents with and without disclosures or assignments to a federal agency are provided in Annexes 4 and 5.

Given the number of contracts and grants from the DoD and HHS to Sarepta, it is highly likely that many of the 91 patents assigned to Sarepta which do not report federal government funding have failed to disclose such funding.

## Remedies for non-disclosure of the eteplirsen patents

The legal issues regarding the obligations to disclose federal funding and the remedies available to the federal government when patents are not timely disclosed are described in the KEI Briefing Note: 2018:1, which is attached to this document.

In the case of the patents to eteplirsen, the most useful action would be for the NIH to take title to the patents that have not disclosed federal funding, and to use the ownership of those patents as leverage to lower the price of Exondys 51, in order to expand access and reduce the financial hardships faced by patients.

## Attachments

“Bayh-Dole Obligations to Disclose Federal Funding in Patented Inventions,” KEI Briefing Note: 2018:1. Andrew Goldman. Revised March 16, 2018.

## Annex 1: Foreign government funding of research

This case illustrates an area for potential future cooperation between the United States and other governments, as regards government rights in patents.

Several foreign governments have funded research that led to the development of Exondys 51.

Academisch Ziekenhuis Leiden, in the Netherlands, is an institution that receives research funding from the Dutch government and the European Union.[12]

The University of Western Australia also reported DMD-related funding from the Western Australia Medical and Health Research Infrastructure Fund (MHRIF).

The European Commission and several other European governments continue to fund research on DMD and many other diseases and conditions. For example, the UK Medical Research Council (MRC) and the National Institute for Health Research (NIHR) supported a clinical trial (NCT00844597) for AVI-4658 (Exondys 51).[13]

> Funded by the Medical Research Council and Sarepta Therapeutics, the consortium designed an early clinical study to obtain critical proof-of-concept data for an antisense oligonucleotide or a 'molecular patch' for DMD. The 'molecular patch' was used to induce exon-skipping of exon 51 in the DMD gene, which is known to lead to the production of functional dystrophin. Increasing the levels of functional dystrophin protein could improve treatment outcomes in patients with DMD who possess the appropriate genotype. . .
>
> Dr Edward Kaye, Chief Medical Officer and Senior Vice President of Sarepta Therapeutics, said: "This partnership helped us to rapidly move forward development of Eteplirsen. The University College London also gave us access to the expertise within the NIHR clinical research infrastructure. As a state of the art research facility, the NIHR Great Ormond Street Biomedical Research Centre provided a single location to analyse samples from multiple sites. This gave us a better handle on data quality and a clearer understanding of the progression of the phase I-II study."

[12] SCOPE-DMD, Project ID: 601573, Funded under: FP7-HEALTH.
[13] Duchenne muscular dystrophy - a stratified approach: NIHR researchers collaborate with industry partners to develop a novel therapy to improve treatment outcomes in DMD patients who possess an appropriate genotype. NIHR.

An agreement among governments on the government financing of biomedical R&D, as has been proposed for the World Health Organization, could include provisions for cross-licensing government rights in patents.

## Annex 2: Sarepta Therapeutics sale of priority review voucher for Exondys 51

In considering the adequacy of the incentives to Sarepta Therapeutics for its investments in drug development, note that Sarepta obtained an FDA priority review voucher (PRV) for Exondys 51, which it sold to Gilead in February 2017 for $125 million.

Sarepta Therapeutics Form 10-Q, June 30, 2017

3. GAIN FROM SALE OF PRIORITY REVIEW VOUCHER In February 2017, the Company entered into an agreement with Gilead Sciences, Inc. (“Gilead”) to sell the Company’s Rare Pediatric Disease Priority Review Voucher (“PRV”). The Company received the PRV when EXONDYS 51 was approved by the FDA for the treatment of patients with DMD amenable to exon 51 skipping. Following the early termination of the applicable waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, in March 2017, the Company completed its sale of the PRV to a subsidiary of Gilead. Pursuant to the Agreement, the subsidiary of Gilead paid the Company $125.0 million, which was recorded as a gain from sale of the PRV as it did not have a carrying value at the time of the sale.

## Annex 3: Excerpts from the license agreement between the University of Western Australia and Sarepta Therapeutics

EX-10.1 2 d511409dex101.htm EX-10.1
Exhibit 10.1
EXECUTION VERSION

**AMENDED AND RESTATED EXCLUSIVE LICENSE AGREEMENT**

**THIS AMENDED AND RESTATED EXCLUSIVE LICENSE AGREEMENT** (“Agreement”) is effective as of November 24, 2008 (the “Effective Date”), and is restated as of this 10th day of April, 2013 (“Restatement Date”) by and between **THE UNIVERSITY OF WESTERN AUSTRALIA,** a body corporate established pursuant to the provisions of The University of Western Australia Act 1911, with offices at 35 Stirling Highway, Crawley, Western Australia 6009 (“UWA”), on the one hand, and **SAREPTA THERAPEUTICS**, with offices at 245 First Street Suite 1800 Cambridge, MA 02142 USA (“Sarepta”) and **Sarepta International CV** (“Sarepta Netherlands,” and collectively with Sarepta, “Licensee”), on the other hand.

. . .

**C.** Licensee is in the process of developing various products for the treatment of muscular dystrophy arising from defects in the dystrophin gene by inducing the skipping of certain exons in such gene for which the Patent Rights and Technical Information may be useful.

**D.** UWA and Licensee entered into a certain Exclusive License Agreement, dated as of the Effective Date (the "Prior License Agreement"), pursuant to which UWA granted to Licensee certain exclusive license rights under certain patent rights and technical information relating to the treatment of Duchenne muscular dystrophy by inducing the skipping of certain specified exons or blocks of exons through the use of certain specified antisense sequences (the "Prior License Rights").

**E.** Licensee and UWA desire to expand the Prior License Rights to allow Licensee to conduct research in the Field of Use, and to develop, manufacture, use and sell Products in the Field of Use, using the Patent Rights and Technical Information (as each term is defined below) in accordance with the terms of this Agreement, and UWA desires to have the Patent Rights and the Technical Information developed, used and commercialized in the Field of Use by Licensee. Other than the rights expressly granted by UWA hereunder within the Field of Use, Licensee acknowledges that UWA shall retain all other rights with respect to the Patent Rights and the Technical Information.

. . .

(c) with respect to the Patent Rights, UWA has been assigned all right, title and interest from the Inventors and UWA is listed as the sole owner of record in the records of the United States Patent and Trademark Office and any foreign patent offices with respect to Patent Rights that consist of applications or registrations with such offices,

. . .

(f) the Patent Rights have been duly prepared, filed, prosecuted, obtained, and maintained in accordance with all applicable laws, rules, and regulations;

(g) to the best of UWA's knowledge, and except as specified on Schedule 3.1, no third party's intellectual property rights would be infringed or misappropriated by the practice of the Patent Rights in general and no third party is infringing or misappropriating the Patent Rights;

## Annex 4: Patents assigned to Antivirals, Inc., AVI BioPharma or Sarepta Therapeutics which either declare government funding or share an assignment to a U.S. government agency

| PAT. NO. | Government Rights | Title |
|---|---|---|
| 9,833,468 | Joint assignment to DHHS | Methods for treating progeroid laminopathies using oligonucleotide analogues targeting human LMNA |
| 9,394,323 | HDTRA1-09-C-0046 and HDTRA1-C-10-0079, DoD | Antisense antiviral compound and method for treating influenza viral infection |
| 9,326,992 | Joint assignment to DHHS | Methods for treating progeroid laminopathies using oligonucleotide analogues targeting human LMNA |
| 8,759,307 | NS 41219, AI 43103, AI 25913 from NIH, HHSN266200400058C, HHS | Oligonucleotide compound and method for treating nidovirus infections |
| 8,697,858 | HDTRA1-09-C-0046 and HDTRA1-C-10-0079, DoD | Antisense antiviral compound and method for treating influenza viral infection |
| 8,357,664 | R01 AI056267, NIH | Antisense antiviral compound and method for treating influenza viral infection |
| 8,168,604 | Joint assignment to Army Medical Research and Materiel Command | Antisense antiviral compounds and methods for treating a filovirus infection |
| 8,030,292 | Joint assignment to Army Medical Research and Materiel Command | Antisense antiviral compounds and methods for treating a filovirus infection |
| 8,030,291 | Joint assignment to Army Medical Research and Materiel Command | Antisense antiviral compounds and methods for treating a filovirus infection |
| 7,582,615 | Joint assignment to DHHS | Antisense antiviral compound and method for treating arenavirus infection |

## Annex 5: Patents assigned to Antivirals, Inc., AVI BioPharma or Sarepta Therapeutics with no disclosures of federal funding

| **PAT. NO.** | Title |
|---|---|
| 9,920,085 | Boronic acid conjugates of oligonucleotide analogues |
| 9,862,946 | Peptide oligonucleotide conjugates |
| 9,790,499 | Functionally-modified oligonucleotides and subunits thereof |
| 9,682,097 | Oligonucleotide analogues targeting human LMNA |
| 9,572,899 | Compositions for enhancing transport of molecules into cells |
| 9,534,220 | Antisense antibacterial method and compound |
| 9,506,058 | Compositions for treating muscular dystrophy |
| 9,499,583 | Antibacterial antisense oligonucleotide and method |
| 9,487,786 | Immunosuppression compound and treatment method |
| 9,469,664 | Oligonucleotide analogues having modified intersubunit linkages and/or terminal groups |
| 9,453,225 | Multiple exon skipping compositions for DMD |
| 9,447,417 | Multiple exon skipping compositions for DMD |
| 9,447,416 | Multiple exon skipping compositions for DMD |
| 9,434,948 | Multiple exon skipping compositions for DMD |
| 9,416,361 | Splice-region antisense composition and method |
| 9,382,536 | Antisense antiviral compounds and methods for treating a filovirus infection |
| 9,347,063 | Oligonucleotide analog and method for treating flavivirus infections |
| 9,278,987 | Functionally-modified oligonucleotides and subunits thereof |
| 9,249,243 | Antibacterial antisense oligonucleotide and method |
| 9,238,042 | Antisense modulation of interleukins 17 and 23 signaling |
| 9,234,198 | Multiple exon skipping compositions for DMD |
| 9,217,148 | Exon skipping compositions for treating muscular dystrophy |
| 9,161,948 | Peptide oligonucleotide conjugates |
| 9,157,081 | Chimeric oligomeric compounds for modulation of splicing |
| 9,068,185 | Antisense modulation of nuclear hormone receptors |
| 9,066,967 | Oligonucleotide analogues targeting human LMNA |
| 8,933,216 | Immunosuppression compound and treatment method |
| 8,906,872 | Antisense antiviral compound and method for treating ssRNA viral infection |
| 8,895,722 | Splice-region antisense composition and method |
| 8,877,725 | Peptide conjugated, inosine-substituted antisense oligomer compound and method |
| 8,871,918 | Multiple exon skipping compositions for DMD |
| 8,865,883 | Multiple exon skipping compositions for DMD |
| 8,835,402 | Compound and method for treating myotonic dystrophy |
| 8,785,410 | Antisense composition and method for treating muscle atrophy |

| | |
|---|---|
| 8,785,407 | Antisense antiviral agent and method for treating ssRNA viral infection |
| 8,779,128 | Oligonucleotide analogues having modified intersubunit linkages and/or terminal groups |
| 8,741,863 | Compound and method for treating myotonic dystrophy |
| 8,703,735 | Antisense antiviral compounds and methods for treating a filovirus infection |
| 8,618,270 | Oligonucleotide analog and method for treating flavivirus infections |
| 8,592,386 | Antisense compositions and methods for modulating contact hypersensitivity or contact dermatitis |
| 8,536,147 | Antibacterial antisense oligonucleotide and method |
| 8,524,684 | Antisense antiviral compounds and methods for treating a filovirus infection |
| 8,524,676 | Method for treating enterovirus or rhinovirus infection using antisense antiviral compounds |
| 8,501,704 | Immunosuppression compound and treatment method |
| 8,501,703 | Chimeric oligomeric compounds for modulation of splicing |
| 8,436,163 | Splice-region antisense composition and method |
| 8,415,313 | Antisense oligomers and methods for inducing immune tolerance and immunosuppression |
| 8,329,668 | Antisense antiviral compound and method for treating picornavirus infection |
| 8,314,072 | Antisense antibacterial method and compound |
| 8,299,206 | Method of synthesis of morpholino oligomers |
| 8,198,429 | Antisense antiviral compounds and methods for treating a filovirus infection |
| 8,129,352 | Antisense antiviral compound and method for treating ssRNA viral infection |
| 8,084,433 | Antisense antiviral compound and method for treating ssRNA viral infection |
| 8,076,476 | Synthesis of morpholino oligomers using doubly protected guanine morpholino subunits |
| 8,067,571 | Antibacterial antisense oligonucleotide and method |
| 8,067,569 | Splice-region antisense composition and method |
| 8,053,420 | Peptide conjugated, inosine-substituted antisense oligomer compound and method |
| 8,008,469 | Antisense compound for inducing immunological tolerance |
| 7,989,608 | Immunomodulatory agents and methods of use |
| 7,943,762 | Oligonucleotide analogs having cationic intersubunit linkages |
| 7,888,012 | Antisense composition and method for treating muscle atrophy |
| 7,884,194 | Soluble HER2 and HER3 splice variant proteins, splice-switching oligonucleotides, and their use in the treatment of disease |
| 7,855,283 | Antisense antiviral compound and method for treating arenavirus infection |
| 7,807,801 | Oligonucleotide analog and method for treating flavivirus infections |
| 7,790,694 | Antisense antibacterial method and compound |
| 7,754,238 | Delivery of microparticle-conjugated drugs for inhibition of stenosis |
| 7,625,873 | Antisense antibacterial method and compound |
| 7,524,829 | Antisense antiviral compounds and methods for treating a filovirus infection |
| 7,507,196 | Antisense antiviral compounds and methods for treating a filovirus infection |
| 7,468,418 | Compositions for enhancing transport of molecules into cells |
| 7,402,574 | Antisense composition and method for treating cancer |

| | |
|---|---|
| 7,264,925 | Method for analysis of oligonucleotide analogs |
| 7,238,675 | Antisense antibacterial method and composition |
| 7,115,583 | Microbubble compositions and methods for oligonucleotide delivery |
| 7,094,765 | Antisense restenosis composition and method |
| 7,049,431 | Antisense antibacterial cell division composition and method |
| 6,869,795 | Antisense compositions and cancer-treatment methods |
| 6,841,542 | Transforming growth factor beta (TGF-.beta.) blocking agent-treated stem cell composition and method |
| 6,828,105 | Antisense antiviral agent and method for treating ssRNA viral infection |
| 6,784,291 | Splice-region antisense composition and method |
| 6,764,680 | Combined approach to treatment of cancer with hCG vaccines |
| 6,677,153 | Antisense antibacterial method and composition |
| 6,365,577 | p53 antisense agent and method |
| 6,365,351 | Non-invasive method for detecting target RNA |
| 6,124,271 | Method and conjugate for treating H. pylori infection |
| 6,060,246 | Reagent and method for isolation and detection of selected nucleic acid sequences |
| 6,030,941 | Polymer composition for delivering substances in living organisms |
| 5,698,685 | Morpholino-subunit combinatorial library and method |
| 5,521,063 | Polynucleotide reagent containing chiral subunits and methods of use |
| 5,506,337 | Morpholino-subunit combinatorial library and method |
| 5,378,841 | Alpha-morpholino ribonucleoside derivatives and polymers thereof |

## Annex 6: Selected exhibits of Sarepta Therapeutics SEC filings

| Description | Form | Exhibit | Filing Date |
|---|---|---|---|
| Agreement between AVI BioPharma, Inc. and the U.S. Defense Threat Reduction Agency dated May 5, 2009. | 10-Q | 10.72 | 8/10/09 |
| Amended and Restated Exclusive License Agreement by and among The University of Western Australia, Sarepta Therapeutics, Inc., and Sarepta International CV dated April 10, 2013. | 10-Q | 10.1 | 5/9/13 |
| Amended and Restated Executive Employment Agreement dated April 19, 2013 by and between Sarepta Therapeutics, Inc. and Christopher Garabedian. | 10-Q | 10.2 | 5/9/13 |
| Amendment No. 1 to the License and Collaboration Agreement between Summit (Oxford) Ltd. and Sarepta Therapeutics Inc. dated June 13, 2017 | 10-Q | 10.1 | 8/3/17 |
| Amendment No. 2 to Employment Agreement with Patrick Iversen, Ph.D., dated January 18, 2010. | 10-K | 10.6 | 3/15/11 |
| Amendment of Contract between AVI BioPharma, Inc. and the U.S. Defense Threat Reduction Agency (contract no HDTRA 1-09-C-0046), effective March 25, 2010. | 10-Q | 10.81 | 5/10/10 |
| Amendment of Contract between AVI BioPharma, Inc. and the U.S. Defense Threat Reduction Agency (contract no. HDTRA 1-07-C0010), effective September 30, 2009. | 10-Q | 10.77 | 11/9/09 |
| Amendment of Contract between AVI BioPharma, Inc. and the U.S. Defense Threat Reduction Agency (contract no. HDTRA1-07-C-0010), effective May 29, 2009. | 10-Q | 10.74 | 8/10/09 |
| Amendment to Employment Agreement with Patrick Iversen, Ph.D., dated December 28, 2008. | 10-K | 10.5 | 3/15/11 |
| Asset Purchase Agreement dated February 20, 2017 by and between Sarepta Therapeutics Inc. and Gilead Sciences, Inc. | 10-Q | 10.1 | 5/4/17 |
| Collaboration and License Agreement between Isis Pharmaceuticals and Ercole Biotech, Inc. dated May 16, 2003. | 10-K | 10.78 | 3/16/10 |
| Consulting Agreement dated August 17, 2017 by and between Sarepta Therapeutics, Inc. and Dr. Edward M. Kaye | 10-Q | 10.1 | 11/1/17 |
| Contract Number HDTRA1-10-C-0079 between Defense Threat Reduction Agency and AVI BioPharma, Inc. dated June 4, 2010. | 10-Q | 10.84 | 8/9/10 |
| Contract Number W9113M-10-C-0056 between U.S. Army Space and Missile Defense Command and AVI BioPharma, Inc. dated July 14, 2010. | 10-Q | 10.86 | 11/9/10 |
| Contract Number W911QY-12-C-0117 between U.S. Department of Defense's Joint Project Manager Transformational Medical Technologies and Sarepta Therapeutics, Inc. dated August 23, 2012. | 10-Q | 10.1 | 11/7/12 |
| Employment Agreement dated September 20, 2016 between Sarepta Therapeutics, Inc. and Edward M. Kaye, M.D. | 10-Q | 10.1 | 11/7/16 |
| Employment Agreement with Patrick Iversen, Ph.D., dated July 14, 1997. | 10KSB | 10.12 | 3/30/98 |

| | | | |
|---|---|---|---|
| Exclusive License Agreement by and between The University of Western Australia and AVI BioPharma, Inc., dated November 24, 2008. | 10-K | 10.36 | 3/15/11 |
| Executive Employment Agreement dated June 13, 2011 by and between AVI BioPharma, Inc. and Edward Kaye, M.D. | 10-Q | 10.4 | 8/8/11 |
| First Amendment to License Agreement by and among The University of Western Australia, Sarepta Therapeutics, Inc., and Sarepta International CV dated June 19, 2016. | 10-Q | 10.1 | 8/9/16 |
| First Amendment to Sponsored Research Agreement between AVI BioPharma, Inc. and Charley's Fund, Inc. dated June 2, 2009. | 10-Q | 10.75 | 8/10/09 |
| License Agreement between Sarepta Therapeutics, Inc. and Sarepta International C.V. on the one hand and BioMarin Leiden Holding BV, BioMarin Nederlands BV and BioMarin Technologies BV on the other hand dated July 17, 2017 | 10-Q | 10.8 | 8/3/17 |
| License and Collaboration Agreement between Summit (Oxford) Ltd and Sarepta Therapeutics, Inc. dated October 3, 2016 | 10-Q | 10.2 | 11/7/16 |
| Modification No. P00005 to Contract Number HDTRA1-10-C-0079 between Defense Threat Reduction Agency and AVI BioPharma, Inc. effective April 13, 2011. | 10-Q | 10.1 | 8/8/11 |
| Modification No. P00005 to Contract Number W9113M-10-C-0056 between U.S. Army Space and Missile Defense Command and AVI BioPharma, Inc. effective August 15, 2011. | 10-Q/A | 10.3 | 2/15/12 |
| Modification No. PZ0001 to Contract Number HDTRA1-10-C-0079 between Defense Threat Reduction Agency and AVI BioPharma, Inc. effective March 3, 2011. | 10-Q | 10.3 | 5/10/11 |
| Settlement Agreement between Sarepta Therapeutics, Inc., Sarepta International C.V. and The University of Western Australia on the one hand, and BioMarin Leiden Holding BV, BioMarin Nederlands BV and BioMarin Technologies BV on the other hand dated July 17, 2017 | 10-Q | 10.7 | 8/3/17 |
| Sponsored Research Agreement between AVI BioPharma, Inc. and Charley's Fund, Inc., effective October 12, 2007. | 10-K | 10.58 | 3/17/08 |